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A61K 31/4995, A61P 13/12 CH-4153 Reinach (CH).

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(71) Applicant (for all designated States except US): **ACTE-
LION PHARMACEUTICALS LTD** [CH/CH]; Gewerbe-
strasse 16, CH-4123 Allschwil (CH).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BEZENCON**,
Olivier [CH/CH]; Dürrenmattweg 53, CH-4123 Allschwil
(CH). **BUR, Daniel** [CH/CH]; Im Rosengarten 24,
CH-4106 Therwil (CH). **FISCHLI, Walter** [CH/CH];
Obertorweg 64, CH-4123 Allschwil (CH). **REMEN**,
Lubos [SK/CH]; Kurzellängeweg 28, CH-4123 Allschwil
(CH). **RICHARD-BILDSTEIN**, Sylvia [FR/FR]; 12, rue
des Beaux Prés, F-68440 Dietwiller (FR). **WELLER**,
Thomas [CH/CH]; Hoezlistrasse 58, CH-4102 Binningen
(CH).

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(54) Title: DIAZABICYCLONONENE AND TETRAHYDROPYRIDINE DERIVATIVES AS RENIN INHIBITORS

(57) Abstract: The invention relates to novel 3,9-diazabicyclo[3.3.1]nonene derivatives, tetrahydropyridine derivatives, and related compounds and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as inhibitors of renin.

DIAZABICYCLONONENE AND
TETRAHYDROPYRIDINE DERIVATIVES AS RENIN INHIBITORS

5

The invention relates to novel compounds of the general formula I. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula I and especially their use as renin inhibitors in cardiovascular events and
10 renal insufficiency. Furthermore, these compounds can be regarded as inhibitors of other aspartyl proteases and might therefore be useful as inhibitors of plasmepsins to treat malaria and as inhibitors of *Candida albicans* secreted aspartyl proteases to treat fungal infections.

15 In the renin-angiotensin system (RAS) the biologically active angiotensin II (Ang II) is generated by a two-step mechanism. The highly specific enzyme renin cleaves angiotensinogen to angiotensin I (Ang I), which is then further processed to Ang II by the less specific angiotensin-converting enzyme (ACE). Ang II is known to work on at least two receptor subtypes called AT₁ and AT₂. Whereas
20 AT₁ seems to transmit most of the known functions of Ang II, the role of AT₂ is still unknown.

Modulation of the RAS represents a major advance in the treatment of cardiovascular diseases. ACE inhibitors and AT₁ blockers have been accepted to
25 treat hypertension (Waeber B. *et al.*, "The renin-angiotensin system: role in experimental and human hypertension", in Berkenhager W. H., Reid J. L. (eds): *Hypertension*, Amsterdam, Elsevier Science Publishing Co, 1996, 489-519; Weber M. A., *Am. J. Hypertens.*, 1992, 5, 247S). In addition, ACE inhibitors are used for renal protection (Rosenberg M. E. *et al.*, *Kidney International*, 1994, 45,
30 403; Breyer J. A. *et al.*, *Kidney International*, 1994, 45, S156), in the prevention of congestive heart failure (Vaughan D. E. *et al.*, *Cardiovasc. Res.*, 1994, 28, 159;

Fouad-Tarazi F. *et al.*, *Am. J. Med.*, **1988**, *84 (Suppl. 3A)*, 83) and myocardial infarction (Pfeffer M. A. *et al.*, *N. Engl. J. Med.*, **1992**, 327, 669).

The rationale to develop renin inhibitors is the specificity of renin (Kleinert H. D., *Cardiovasc. Drugs*, **1995**, *9*, 645). The only substrate known for renin is angiotensinogen, which can only be processed (under physiological conditions) by renin. In contrast, ACE can also cleave bradykinin besides Ang I and can be bypassed by chymase, a serine protease (Husain A., *J. Hypertens.*, **1993**, *11*, 1155). In patients inhibition of ACE thus leads to bradykinin accumulation causing cough (5-20%) and potentially life-threatening angioneurotic edema (0.1-0.2%) (Israili Z. H. *et al.*, *Annals of Internal Medicine*, **1992**, *117*, 234). Chymase is not inhibited by ACE inhibitors. Therefore, the formation of Ang II is still possible in patients treated with ACE inhibitors. Blockade of the AT₁ receptor (e.g. by losartan) on the other hand overexposes other AT-receptor subtypes to Ang II, whose concentration is dramatically increased by the blockade of AT₁ receptors. This may raise serious questions regarding the safety and efficacy profile of AT₁ receptor antagonists. In summary, renin inhibitors are not only expected to be different from ACE inhibitors and AT₁ blockers with regard to safety, but more importantly also with regard to their efficacy to block the RAS.

Only limited clinical experience (Azizi M. *et al.*, *J. Hypertens.*, **1994**, *12*, 419; Neutel J. M. *et al.*, *Am. Heart*, **1991**, *122*, 1094) has been created with renin inhibitors because of their insufficient oral activity due to their peptidomimetic character (Kleinert H. D., *Cardiovasc. Drugs*, **1995**, *9*, 645). The clinical development of several compounds has been stopped because of this problem together with the high cost of goods. Only one compound containing four chiral centers has entered clinical trials (Rahuel J. *et al.*, *Chem. Biol.*, **2000**, *7*, 493; Mealy N. E., *Drugs of the Future*, **2001**, *26*, 1139). Thus, metabolically stable, orally bioavailable and sufficiently soluble renin inhibitors that can be prepared on a large scale are missing and sought. Recently, the first non-peptide renin inhibitors were described which show high *in vitro* activity (Oefner C. *et al.*, *Chem. Biol.*, **1999**, *6*, 127; Patent Application WO97/09311; Märki H. P. *et al.*, *Il*

Farmaco, 2001, 56, 21). However, the development status of these compounds is not known.

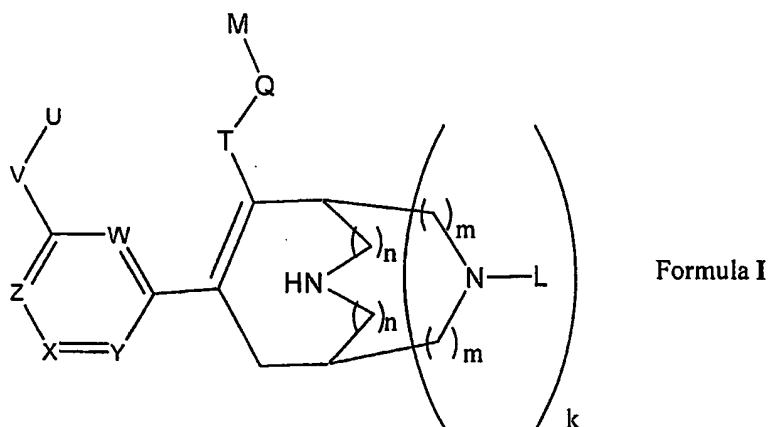
The present invention relates to the identification of renin inhibitors of a non-peptidic nature and of low molecular weight. Orally active renin inhibitors of long duration of action which are active in indications beyond blood pressure regulation where the tissular renin-chymase system may be activated leading to pathophysiologically altered local functions such as renal, cardiac and vascular remodeling, atherosclerosis, and possibly restenosis are described.

10

The present invention describes non-peptidic renin inhibitors.

In particular, the present invention relates to novel compounds of the general formula I,

15



wherein

20 Z, Y, X and W represent independently a nitrogen atom or a -CH- group; at least two of the Z, Y, X and W represent a -CH- group;

V represents a bond; $-(CH_2)_1-$; $-A-(CH_2)_5-$; $-CH_2-A-(CH_2)_1-$; $-(CH_2)_5-A-$; $-(CH_2)_2-A-(CH_2)_4-$; $-A-(CH_2)_4-B-$; $-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-$; $-CH_2-$
 25 $A-CH_2-CH_2-B-$; $-CH_2-CH_2-CH_2-A-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2-A-CH_2-$; $-A-$

CH₂-CH₂-B-CH₂-CH₂-; -CH₂-A-CH₂-CH₂-B-CH₂-; -CH₂-A-CH₂-CH₂-CH₂-B-; or
-CH₂-CH₂-A-CH₂-CH₂-B-;

A and B independently represent -O-; -S-; -SO-; -SO₂-;

5

U represents aryl; heteroaryl;

T represents -CONR¹-; -(CH₂)_pOCO-; -(CH₂)_pN(R¹)CO-; -(CH₂)_pN(R¹)SO₂-; or
-COO-;

10

Q represents lower alkylene; lower alkenylene;

M represents hydrogen; cycloalkyl; aryl; heterocyclyl; heteroaryl;

15 L represents -R³; -COR³; -COOR³; -CONR²R³; -SO₂R³; -SO₂NR²R³;
-COCH(Aryl)₂;

R¹ represents hydrogen; lower alkyl; lower alkenyl; lower alkynyl; cycloalkyl;
aryl; cycloalkyl - lower alkyl;

20

R² and R^{2'} independently represent hydrogen; lower alkyl; lower alkenyl;
cycloalkyl; cycloalkyl - lower alkyl;

R³ represents hydrogen; lower alkyl; lower alkenyl; cycloalkyl; aryl; heteroaryl;
25 heterocyclyl; cycloalkyl - lower alkyl; aryl - lower alkyl; heteroaryl - lower alkyl;
heterocyclyl - lower alkyl; aryloxy - lower alkyl; heteroaryloxy - lower alkyl,
whereby these groups may be unsubstituted or mono-, di- or trisubstituted with
hydroxy, -OCOR², -COOR², lower alkoxy, cyano, -CONR²R^{2'}, -CO-morpholin-4-
yl, -CO-((4-loweralkyl)piperazin-1-yl), -NH(NH)NH₂, -NR⁴R^{4'} or lower alkyl,
30 with the proviso that a carbon atom is attached at the most to one heteroatom in
case this carbon atom is sp³-hybridized;

R^4 and $R^{4'}$ independently represent hydrogen; lower alkyl; cycloalkyl; cycloalkyl - lower alkyl; hydroxy - lower alkyl; $-\text{COOR}^2$; $-\text{CONH}_2$;

k is the integer 0 or 1;

5

m and n represent the integer 0 or 1, with the proviso that in case m represents the integer 1, n is the integer 0; in case n represents the integer 1, m is the integer 0; in case k represents the integer 0, n represents the integer 0;

- 10 p is the integer 1, 2, 3 or 4;
r is the integer 1, 2, 3, 4, 5, or 6;
s is the integer 1, 2, 3, 4, or 5;
t is the integer 1, 2, 3, or 4;
u is the integer 1, 2, or 3;
15 v is the integer 2, 3, or 4;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically
20 acceptable salts, solvent complexes and morphological forms.

In the definitions of general formula I – if not otherwise stated – the term **lower alkyl**, alone or in combination with other groups, means saturated, straight and branched chain groups with one to seven carbon atoms, preferably one to four
25 carbon atoms that can be optionally substituted by halogens. Examples of lower alkyl groups are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl and heptyl. The methyl, ethyl and isopropyl groups are preferred.

30 The term **lower alkoxy** refers to a R-O-group, wherein R is a lower alkyl. Examples of lower alkoxy groups are methoxy, ethoxy, propoxy, iso-propoxy, isobutoxy, sec-butoxy and tert-butoxy.

The term **lower alkenyl**, alone or in combination with other groups, means straight and branched chain groups comprising an olefinic bond and consisting of two to seven carbon atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkenyl are vinyl, propenyl
5 or butenyl.

The term **lower alkynyl**, alone or in combination with other groups, means straight and branched chain groups comprising a triple bond and consisting of two to seven carbon atoms, preferably two to four carbon atoms, that can be optionally
10 substituted by halogens. Examples of lower alkynyl are ethynyl, propynyl or butynyl.

The term **lower alkylene**, alone or in combination with other groups, means straight and branched divalent chain groups with one to seven carbon atoms, preferably one to four carbon atoms, that can be optionally substituted by
15 halogens. Examples of lower alkylene are ethylene, propylene or butylene.

The term **lower alkenylene**, alone or in combination with other groups, means straight and branched divalent chain groups comprising an olefinic bond and consisting of two to seven carbon atoms, preferably two to four carbon atoms, that
20 can be optionally substituted by halogens. Examples of lower alkenylene are vinylene, propenylene and butenylene.

The term **lower alkylenedioxy**, refers to a lower alkylene substituted at each end
25 by an oxygen atom. Examples of lower alkylenedioxy groups are preferably methylenedioxy and ethylenedioxy.

The term **lower alkylenoxy** refers to a lower alkylene substituted at one end by an oxygen atom. Examples of lower alkylenoxy groups are preferably methylenoxy,
30 ethylenoxy and propylenoxy.

The term **halogen** means fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine and bromine.

The term **cycloalkyl** alone or in combination, means a saturated cyclic hydrocarbon ring system with 3 to 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, which can be optionally mono- or multisubstituted by lower alkyl, lower alkenyl, lower alkenylene, lower alkoxy, lower alkylendioxy, lower alkylendioxy, hydroxy, halogen, $-\text{CF}_3$, $-\text{NR}^1\text{R}^{1'}$, $-\text{NR}^1\text{C}(\text{O})\text{R}^{1'}$, $-\text{NR}^1\text{S}(\text{O}_2)\text{R}^{1'}$, $-\text{C}(\text{O})\text{NR}^1\text{R}^{1'}$, lower alkylcarbonyl, $-\text{COOR}^1$, $-\text{SR}^1$, $-\text{SOR}^1$, $-\text{SO}_2\text{R}^1$, $-\text{SO}_2\text{NR}^1\text{R}^{1'}$ whereby $\text{R}^{1'}$ represents hydrogen; lower alkyl; lower alkenyl; lower alkynyl; cycloalkyl; aryl; cycloalkyl - lower alkyl. The cyclopropyl group is a preferred group.

The term **aryl**, alone or in combination, relates to the phenyl, the naphthyl or the indanyl group, preferably the phenyl group, which can be optionally mono- or multisubstituted by lower alkyl, lower alkenyl, lower alkynyl, lower alkenylene or lower alkylene forming with the aryl ring a five- or six-membered ring, lower alkoxy, lower alkylendioxy, lower alkylendioxy, hydroxy, hydroxy-lower alkyl, halogen, cyano, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{NR}^1\text{R}^{1'}$, $-\text{NR}^1\text{R}^{1'}$ - lower alkyl, $-\text{NR}^1\text{C}(\text{O})\text{R}^{1'}$, $-\text{NR}^1\text{S}(\text{O}_2)\text{R}^{1'}$, $-\text{C}(\text{O})\text{NR}^1\text{R}^{1'}$, $-\text{NO}_2$, lower alkylcarbonyl, $-\text{COOR}^1$, $-\text{SR}^1$, $-\text{SOR}^1$, $-\text{SO}_2\text{R}^1$, $-\text{SO}_2\text{NR}^1\text{R}^{1'}$, benzyloxy, whereby $\text{R}^{1'}$ has the meaning given above.

The term **aryloxy** refers to an Ar-O-group, wherein Ar is an aryl. An example of a lower aryloxy group is phenoxy.

25

The term **heterocyclyl**, alone or in combination, means saturated or unsaturated (but not aromatic) five-, six- or seven-membered rings containing one or two nitrogen, oxygen or sulfur atoms which may be the same or different and which rings can be optionally substituted with lower alkyl, hydroxy, lower alkoxy and halogen. The nitrogen atoms, if present, can be substituted by a $-\text{COOR}^2$ group. Examples of such rings are piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, 1,4-dioxanyl, pyrrolidinyl,

tetrahydrofuranyl, dihydropyrrolyl, imidazolidinyl, dihydropyrazolyl, pyrazolidinyl, dihydroquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl.

The term **heteroaryl**, alone or in combination, means six-membered aromatic rings containing one to four nitrogen atoms; benzofused six-membered aromatic rings containing one to three nitrogen atoms; five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; benzofused five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; five-membered aromatic rings containing one oxygen and one nitrogen atom and benzofused derivatives thereof; five-membered aromatic rings containing a sulfur and a nitrogen or an oxygen atom and benzofused derivatives thereof; five-membered aromatic rings containing two nitrogen atoms and benzofused derivatives thereof; five-membered aromatic rings containing three nitrogen atoms and benzofused derivatives thereof, or a tetrazolyl ring. Examples of such ring systems are furanyl, thiophenyl, pyrrolyl, pyridinyl, pyrimidinyl, indolyl, quinolinyl, isoquinolinyl, imidazolyl, triazinyl, thiazinyl, thiazolyl, isothiazolyl, pyridazinyl, pyrazolyl, oxazolyl, isoxazolyl, coumarinyl, benzothiophenyl, quinazolinyl, quinoxalinyl. Such rings may be adequately substituted with lower alkyl, lower alkenyl, lower alkynyl, lower alkylene, lower alkenylene, lower alkylenedioxy, lower alkyleneoxy, hydroxy-lower alkyl, lower alkoxy, hydroxy, halogen, cyano, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{NR}^1\text{R}^{1'}$, $-\text{NR}^1\text{R}^{1'}$ - lower alkyl, $-\text{N}(\text{R}^1)\text{COR}^1$, $-\text{N}(\text{R}^1)\text{SO}_2\text{R}^1$, $-\text{CONR}^1\text{R}^{1'}$, $-\text{NO}_2$, lower alkylcarbonyl, $-\text{COOR}^1$, $-\text{SR}^1$, $-\text{SOR}^1$, $-\text{SO}_2\text{R}^1$, $-\text{SO}_2\text{NR}^1\text{R}^{1'}$, another aryl, another heteroaryl or another heterocyclyl and the like, whereby $\text{R}^{1'}$ has the meaning given above.

25

The term **heteroaryloxy** refers to a Het-O-group, wherein Het is a heteroaryl.

The term **sp³-hybridized** refers to a carbon atom and means that this carbon atom forms four bonds to four substituents placed in a tetragonal fashion around this carbon atom.

30

The expression **pharmaceutically acceptable** salts encompasses either salts with inorganic acids or organic acids like hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, benzoic acid, methanesulfonic acid, p-toluenesulfonic acid, and the like that
5 are non toxic to living organisms or in case the compound of formula I is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide and the like.

Compounds of the invention also include nitrosated compounds of the general
10 formula I that have been nitrosated through one or more sites such as oxygen (hydroxyl condensation), sulfur (sulffiydryl condensation) and/or nitrogen. The nitrosated compounds of the present invention can be prepared using conventional methods known to one skilled in the art. For example, known methods for nitrosating compounds are described in U.S. Pat. Nos. 5,380,758 and 5,703,073;
15 WO 97/27749; WO 98/19672; WO 98/21193; WO 99/00361 and Oae et al, Org. Prep. Proc. Int., 15(3):165-198 (1983), the disclosures of each of which are incorporated by reference herein in their entirety.

The compounds of the general formula I can contain two or more asymmetric
20 carbon atoms and may be prepared in form of optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form and pharmaceutically acceptable salts thereof.

The present invention encompasses all these forms. Mixtures may be separated in
25 a manner known *per se*, i.e. by column chromatography, thin layer chromatography, HPLC or crystallization.

A group of preferred compounds are compounds of general formula I wherein Z,
Y, X, W, V, U, T, Q, L, and M are as defined in general formula I above and
30 wherein

k is 1

n is 0 and

m is 1.

Another group of preferred compounds of general formula I are those wherein Z,
5 Y, X, W, V, U, T, Q, M, k, m, and n are as defined in general formula I above and

L represents H; $-\text{COR}^{3''}$; $-\text{COOR}^{3''}$; $-\text{CONR}^{2''}\text{R}^{3''}$;

whereby $\text{R}^{2''}$ and $\text{R}^{3''}$ represent independently lower alkyl, lower cycloalkyl -
10 lower alkyl, which lower alkyl and lower cycloalkyl - lower alkyl groups are
unsubstituted or monosubstituted with halogen, cyano, hydroxy, $-\text{OCOCH}_3$,
 $-\text{CONH}_2$, $-\text{COOH}$ or $-\text{NH}_2$, with the proviso that a carbon atom is attached at the
most to one heteroatom in case this carbon atom is sp^3 -hybridized.

15 Another group of preferred compounds of general formula I above are those
wherein Z, Y, X, W, V, U, L, k, m, and n are as defined in general formula I and

T is $-\text{CONR}^1$;

Q is methylene;

20 M is aryl; heteroaryl.

Another group of also more preferred compounds of general formula I are those
wherein V, U, T, Q, M, L, k, m, and n are as defined in general formula I above
and

25

Z, Y, X and W represent $-\text{CH}-$.

Another group of also more preferred compounds of general formula I are those
wherein Z, Y, X, W, V, Q, T, M, L, k, m, and n are as defined in general formula I
30 above and

U is a mono-, di-, or trisubstituted phenyl or heteroaryl, wherein the substituents are halogen, lower alkyl, lower alkoxy, CF₃.

Especially preferred compounds of general formula I are those selected from the
5 group consisting of:

(*rac.*)-(1*R**, 5*S**)-(3-acetyl-7-{3-[2-(2-bromo-5-fluorophenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid methylphenethylamide;

10 (*rac.*)-(1*R**, 5*S**)-3-acetyl-7-{3-[2-(2-chlorophenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid methylphenethylamide;

(*rac.*)-(1*R**, 5*S**)-3-acetyl-7-{3-[2-(2-*tert*-butylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid methylphenethylamide;

15 (*rac.*)-(1*R**, 5*S**)-3-acetyl-7-{3-[2-(2,3,6-trifluorophenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid methylphenethylamide;

(*rac.*)-(1*R**, 5*S**)-3-acetyl-7-{3-[2-(2,5-difluorophenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid methylphenethylamide;

20 (*rac.*)-(1*R**, 5*S**)-3-acetyl-7-[3-(2-*o*-tolylloxyethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid methylphenethylamide;

(*rac.*)-(1*R**, 5*S**)-3-acetyl-7-{3-[2-(2,3-dichlorophenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid methylphenethylamide;

25 (*rac.*)-(1*R**, 5*S**)-3-acetyl-7-{3-[2-(2-chloro-5-methylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid methylphenethylamide;

30 (*rac.*)-(1*R**, 5*S**)-3-acetyl-7-{3-[2-(3-chlorophenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid methylphenethylamide;

- (*rac.*)-(1*R**, 5*S**)-3-acetyl-7-{3-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid methylphenethylamide;
- (*rac.*)-(1*R**, 5*S**)-3-acetyl-7-{3-[2-(2-chlorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid methylphenethylamide;
- (*rac.*)-(1*R**, 5*S**)-3-acetyl-7-{3-[2-(2-*tert*-butylphenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid methylphenethylamide;
- 10 (*rac.*)-(1*R**, 5*S**)-3-acetyl-7-{3-[2-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid methylphenethylamide;
- (*rac.*)-(1*R**, 5*S**)-3-acetyl-7-{3-[2-(2,5-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid methylphenethylamide;
- 15 (*rac.*)-(1*R**, 5*S**)-3-acetyl-7-{3-(2-*o*-tolylloxypropyl)phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid methylphenethylamide;
- (*rac.*)-(1*R**, 5*S**)-3-acetyl-7-{3-[2-(2,3-dichlorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid methylphenethylamide;
- 20 (*rac.*)-(1*R**, 5*S**)-3-acetyl-7-{3-[2-(2-chloro-5-methylphenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid methylphenethylamide;
- (*rac.*)-(1*R**, 5*S**)-3-acetyl-7-{3-[2-(3-chlorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid methylphenethylamide;
- 25 (*rac.*)-(1*R**, 5*S**)-3-acetyl-7-{3-[2-(4-chlorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid methylphenethylamide;
- (*rac.*)-(1*R**, 5*S**)-7-{3-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;
- 30

(*rac.*)-(1*R**, 5*S**)-7-{3-[4-(2-fluoro-3-trifluoromethylphenoxy)butoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

5

(*rac.*)-(1*R**, 5*S**)-7-{3-[4-(2,6-dichloro-4-methylphenoxy)butoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide; and

10 (*rac.*)-(1*R**, 5*S**)-7-{3-[4-(2-chloro-6-fluoro-3-methylphenoxy)butoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide.

The compounds of general formula I and their pharmaceutically acceptable salts
15 may be used as therapeutics e.g. in form of pharmaceutical compositions. These pharmaceutical compositions containing at least one compound of general formula I and usual carrier materials and adjuvants may especially be used in the treatment or prophylaxis of disorders which are associated with a dysregulation of the renin angiotensin system (RAS), comprising cardiovascular and renal diseases.
20 Examples of such diseases are hypertension, congestive heart failure, pulmonary heart failure, coronary diseases, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, and renal failure. They can also be used to prevent restenosis after balloon or stent angioplasty, to treat erectile dysfunction, glomerulonephritis, renal colic, and glaucoma. Furthermore, they can be used in
25 the therapy and the prophylaxis of diabetic complications, complications after vascular or cardiac surgery, complications of treatment with immunosuppressive agents after organ transplantation, complications of cyclosporin treatment, as well as other diseases presently known to be related to the RAS.

30 In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases which are related to the RAS comprising hypertension, congestive heart failure, pulmonary hypertension, cardiac insufficiency, renal

insufficiency, renal or myocardial ischemia, atherosclerosis, renal failure, erectile dysfunction, glomerulonephritis, renal colic, glaucoma, diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of treatment with immunosuppressive agents after organ transplantation, and other
5 diseases which are related to the RAS, which method comprises administering a compound according to general formula I to a human being or animal.

The invention further relates to the use of compounds of general formula I as defined above for the treatment and/or prophylaxis of disorders which are
10 associated with the Renin Angiotensin System (RAS) comprising hypertension, congestive heart failure, pulmonary hypertension, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, renal failure, erectile dysfunction, glomerulonephritis, renal colic, glaucoma, diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of
15 treatment with immunosuppressive agents after organ transplantation, and other diseases known to be related to the RAS.

In addition, the invention relates to the use of compounds as defined above for the preparation of medicaments for the treatment and/or prophylaxis of diseases
20 which are associated with the RAS such as hypertension, coronary diseases, cardiac insufficiency, renal insufficiency, renal and myocardial ischemia, and renal failure.

The compounds of formula I may also be used in combination with one or more
25 other pharmacologically active compounds comprising ACE inhibitors, angiotensin II receptor antagonists, endothelin receptor antagonists, vasodilators, calcium antagonists, potassium activators, diuretics, sympatholitics, beta-adrenergic antagonists, alpha-adrenergic antagonists, and neutral endopeptidase inhibitors, for the treatment of the above-mentioned diseases or disorders.

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All forms of prodrugs leading to an active component comprised by general formula I above are included in the present invention.

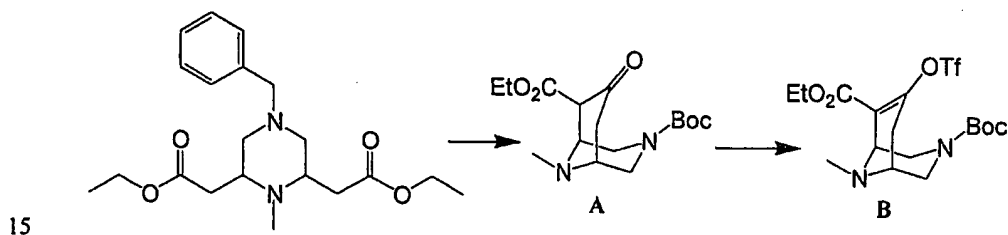
The compounds of general formula I can be manufactured by the methods outlined below, by the methods described in the examples or by analogous methods.

Preparation of the precursors:

Precursors are compounds which were prepared as key intermediates and/or building blocks and which were suitable for further transformations in parallel chemistry.

Bicyclononanone **A** was prepared from (4-benzyl-6-ethoxycarbonylmethyl-1-methylpiperazin-2-yl)acetic acid ethyl ester (Patent Application WO92/05174) as described in Scheme 1. Derivative **A** might also be present as enol form. In order to allow a coupling at the 7-position of bicyclononanone **A** with aryl bromides, the vinyl triflate derivative **B** was prepared.

Scheme 1

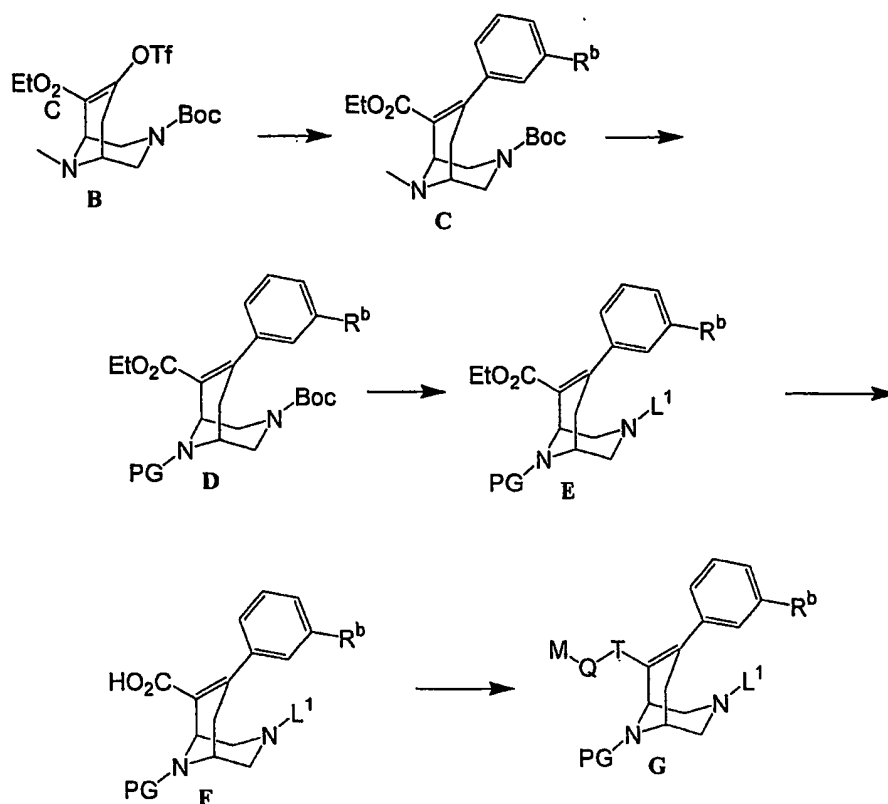


Compound **B** can be then transformed into compounds of type **C** by a *Negishi* coupling (Scheme 2), whereas R^b represents a side chain precursor suitable to construct the V-U-chain through one or several elementary chemical transformations. The R^b -substituent can be modified during the synthesis. After protecting group manipulations leading to compounds of type **D** the L^1 -substituent can be put in place (compounds of type **E**), whereas L^1 represents a substituent L as defined in general formula I, or a precursor of such a substituent. The ester functional group can be saponified to compounds of type **F**. After an amide coupling for instance precursors of type **G** can be obtained.

20

25

Scheme 2



- 5 Other type of compounds described in the general formula I can be prepared using the chemistry described in patent application WO03/093267.

Otherwise heterocyclic systems may be prepared according to the literature existing for similar compounds. For instance pyridine derivative H could be prepared from 2,6-dibromopyridine, wherein R^a is a substituent that may be easily transformed into a chain U-V as described in Formula I (Scheme 3; Bitman, R., et al.; *J. Org. Chem.*, **2000**, 65, 7634). Pyridine J could be prepared by addition of a Grignard reagent on 4-bromopyridine, followed by oxidation (see Comins, D.; et al.; *J. Org. Chem.*, **1985**, 50, 4410). From known 3,5-dibromopyridine a compound of type K could be prepared. Finally pyridines of type L could be prepared from commercially available 2-(pyridin-4-yl)-alcohol, according to the

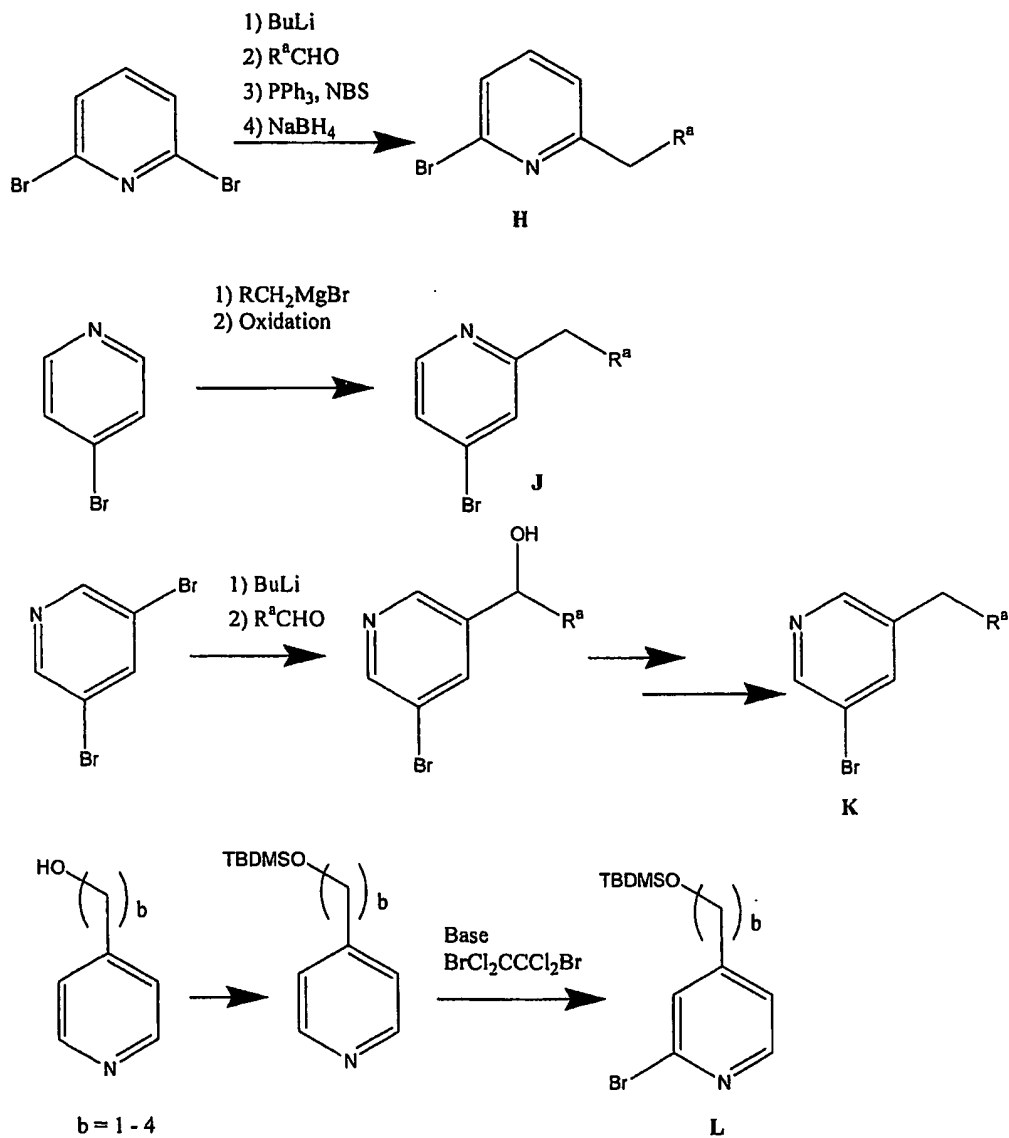
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literature described for similar compounds (Taylor, S. L.; et. al.; *J. Org. Chem.*, 1983, 48, 4156).

Scheme 3

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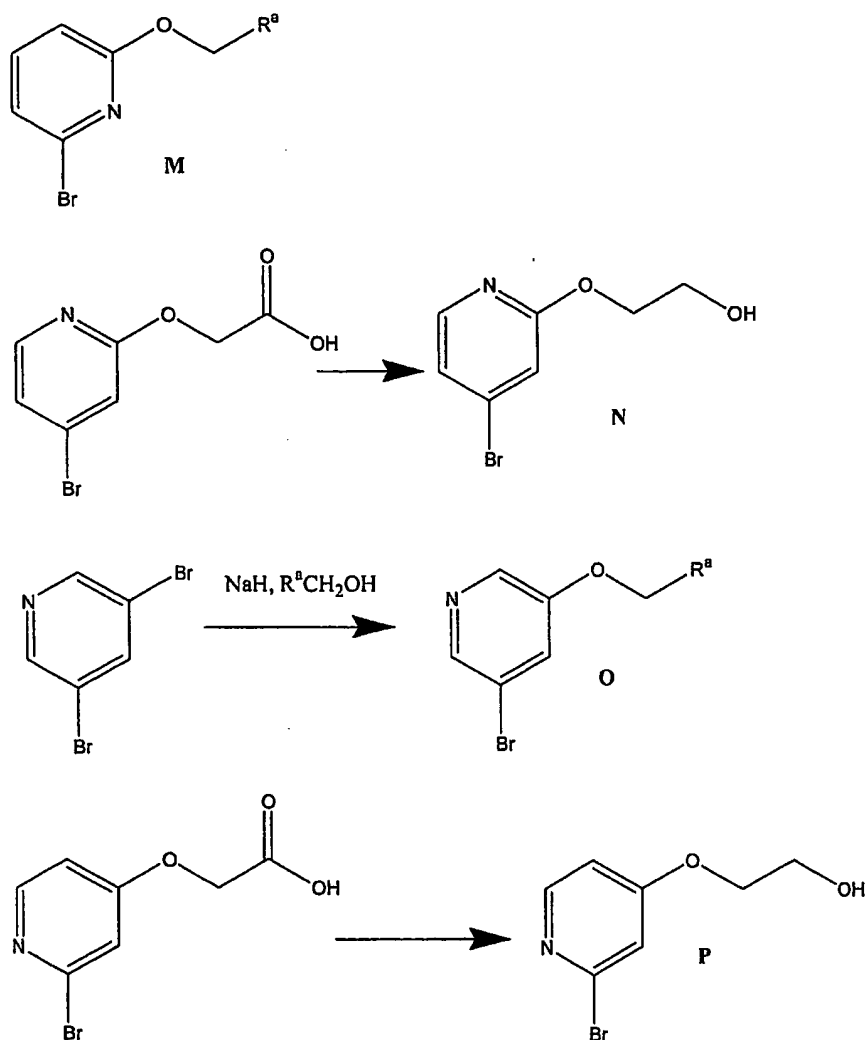


Pyridine derivatives of type **M** could be prepared according to the literature (Scheme 4, Newkome, G. R.; et al.; *J. Am. Chem. Soc.*, 1975, 97, 3232). Known
 10 (4-bromopyridin-2-yloxy)acetic acid could lead to compound **N** by reduction. Compounds of type **O** could be prepared from 3,5-dibromopyridine, according to

Harrowven, D. C.; et al.; *Tetrahedron*, **2001**, *57*, 4447. Known (2-bromopyridin-4-yl)acetic acid (Den Hertog, H. J.; et al.; *Chem. Pharm. Bull.*, **1975**, *23*, 3008) could lead to compound P by reduction as well.

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Scheme 4



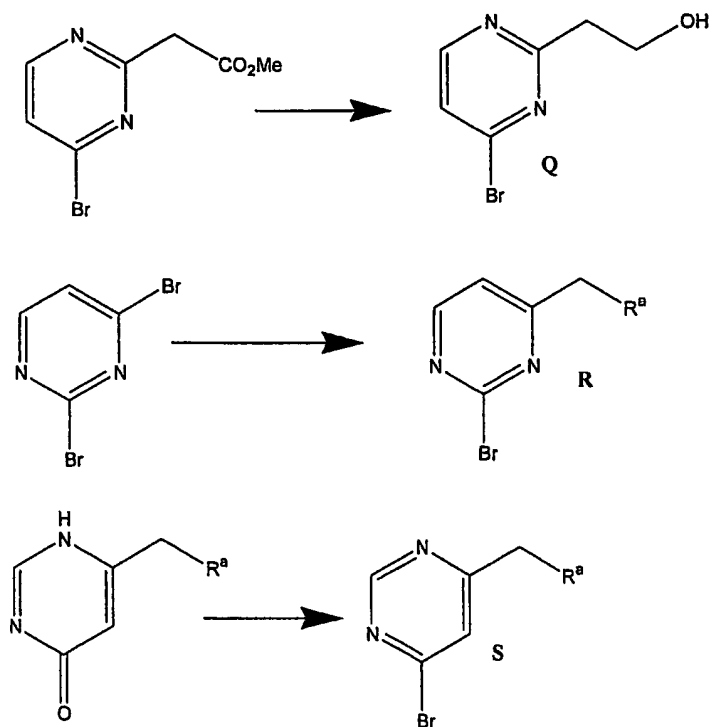
A reduction of the known (4-bromopyrimidin-2-yl)acetic acid methyl ester (Brown, D. J.; et al.; *Australian J. Chem.*, **1978**, *31*, 649) could lead to the desired pyrimidine intermediate Q (Scheme 5). As well, a palladium-catalyzed coupling could transform 2,4-dibromopyrimidine into a compound of type R (see

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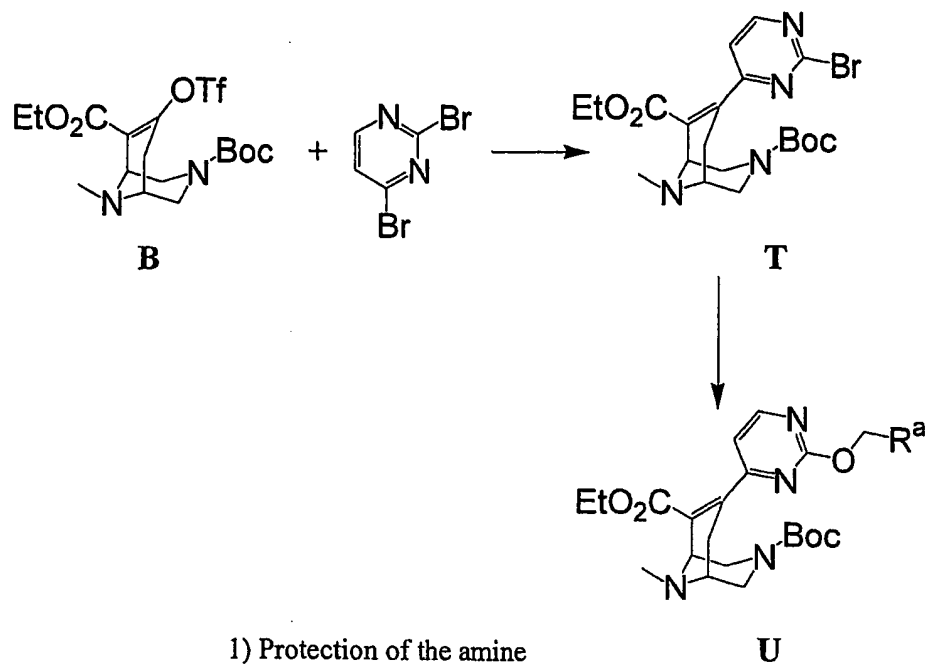
Gronowitz, S.; et al.; *Chem. Scripta*, 1986, 26, 305). Also, compounds of type S could be prepared from 6-alkyl-1H-pyrimidin-4-one.

Scheme 5

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A palladium-catalyzed coupling of 2,4-dibromopyrimidine with bicyclononene **B** could lead to an intermediate of type **T**, which could be transformed into an intermediate of type **U** (Scheme 6). 6-Chloropyrazin-2-ylamine could be transformed in several steps into a pyrazine of type **V** (see Ghosh, A. K.; et al.; *J. Med. Chem.*, 1993, 36, 2300 or Jovanovic, M. V., *Heterocycles*, 1983, 20, 2011, or Hartman, G. D.; et al.; *J. Heterocyclic Chem.*; 1983, 20, 1089). Pyrimidines of type **W** could be prepared according to standard procedures. Finally a compounds of type **X** can be prepared from 4,6-dichloropyrimidine.

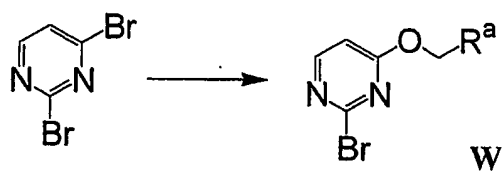
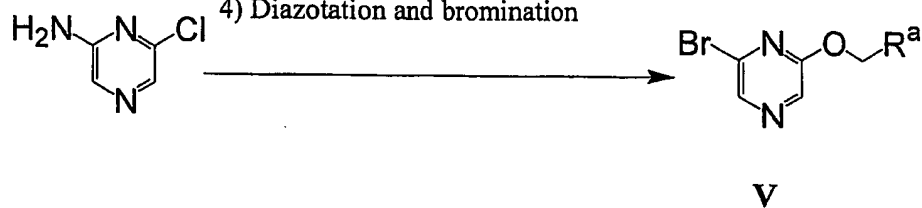
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Scheme 6

1) Protection of the amine

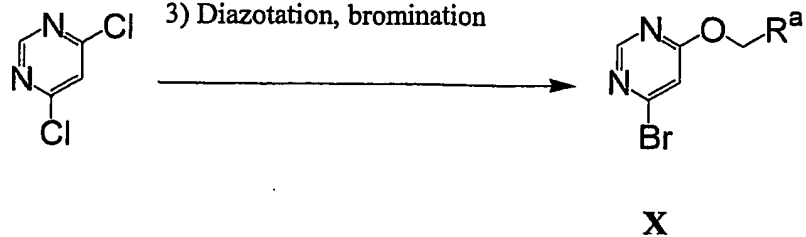
2) $\text{R}^a\text{CH}_2\text{OH}$

3) Deprotection of the amine

4) Diazotation and bromination

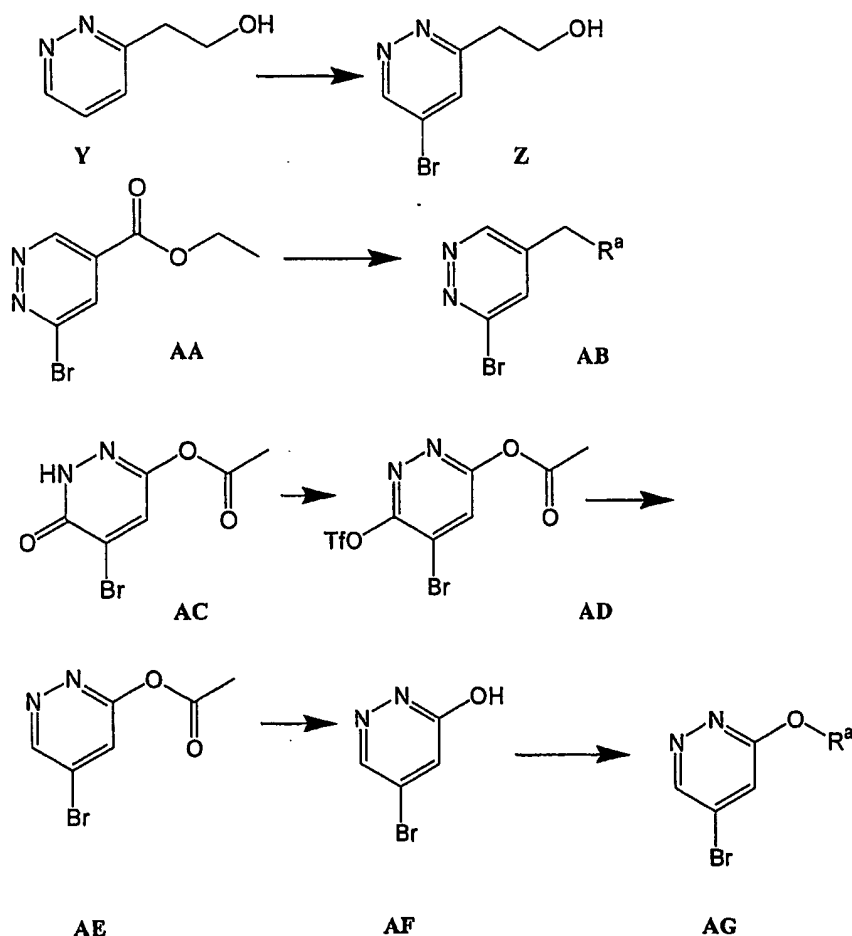
1) $\text{R}^a\text{CH}_2\text{OH}$ 2) NH_3

3) Diazotation, bromination



Pyridazinyl derivatives may be prepared as described in Scheme 7. For instance known 2-pyridazin-3-ylethanol **Y** (Rodriguez, L.; *et al.*; *Synlett*, 1990, 227) could be transformed into a pyridazinyl derivative **Z** following known chemistry (Sauer, J.; *et al.*; *Tetrahedron*, 1998, 54, 4297). Known 6-bromo-pyridazine-4-carboxylic acid ethyl ester **AA** (Dulayyi, A.; *et al.*; *Tetrahedron*, 1998, 54, 12897; Barlin, G. B.; *et al.*; *Australian J. Chem.*, 1977, 30, 2319) could be alkylated, then reduced to a derivative **AB** bearing the desired R^a-substituent. Also, known compound **AC** (Brundish, D. E.; *et al.*; *J. Labelled Compounds and Radiopharmaceuticals*, 1988, 25, 1371) could be transformed to derivative **AD** that could be reduced to pyridazinyl derivative **AE**. Hydrolysis could lead to derivative **AF**, finally O-alkylation to the desired intermediate **AG**.

Scheme 7

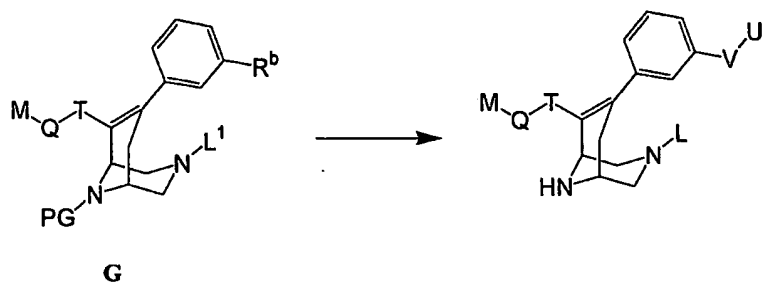


Preparation of final compounds

Precursors **G** were transformed into the corresponding aryl ethers (Scheme 8), using the *Mitsunobu* reaction conditions. After deprotection, the final compounds are obtained.

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Scheme 8



- 10 The compounds of formula **I** and their pharmaceutically acceptable acid addition salts can be used as medicaments, e. g. in the form of pharmaceutical preparations for enteral, parenteral, or topical administration. They can be administered, for example, perorally, e. g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e. g. in the form of suppositories, parenterally, e. g. in the form of injection solutions or infusion solutions, or topically, e. g. in the form of ointments, creams or oils.
- 15

The production of pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula **I** and their pharmaceutically acceptable acid addition salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

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Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated